

Use of Cerny Epoxides for the Accelerated Synthesis of Glycosaminoglycans

- Supporting Information -

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General Methods:

Chemicals and reagents were used without further purification unless otherwise noted. If necessary, reactions were performed under argon atmosphere using anhydrous solvents. Thin layer chromatography was performed using E. Merck silica gel 60 F254 precoated plates and visualized using cerium ammonium molybdate stain. Flash column chromatography was carried out with Silica Gel 60 (230-400 mesh). NMR spectra were obtained on a Varian Mercury 300 instrument. High resolution mass spectra were obtained with a Jeol JMS-600H spectrometer.

1,6:2,3-Dianhydro-4-O-*p*-methoxybenzyl- β -D-mannopyranose (2):

The iodide **1**¹ (500 mg, 1.84 mmol), twice evaporated from acetonitrile, was dissolved in DMF (10 mL) and cooled to -20 °C. *p*-Methoxybenzyl chloride (720 mg, 4.60 mmol) and NaH (147 g, 3.68 mmol, 60% in mineral oil) were added. The reaction mixture was stirred for 2 h (-20 °C → r.t.). Water was added carefully and the mixture was diluted with Et₂O. The aqueous layer was extracted four times with Et₂O. The combined organic layers were washed with brine, dried with MgSO₄, filtered and the solvent was removed in vacuo. Flash chromatography on silica gel (hexanes/EtOAc 1:1) afforded epoxide **2** (365 mg, 1.38 mmol, 75%) as a colorless oil.

¹H NMR (300 MHz, CDCl₃): δ 7.28 (d, *J* = 8.9 Hz, 2H, arom.), 6.87 (d, *J* = 8.9 Hz, 2H, arom.), 5.68 (d, *J* = 3.3 Hz, 1H, 1-H), 4.64 (s, 2H, bz), 4.45 (d, *J* = 6.6 Hz, 1H, 5-H), 3.78 (s, 3H, OMe), 3.69-3.61 (m, 3H, 4-H, 6-H₂), 3.14 (dd, *J* = 3.3, 3.3 Hz, 1H, 2-H), 3.13 (d, *J* = 3.3 Hz, 1H, 3-H).

¹³C NMR (75 MHz, CDCl₃): δ 159.2, 129.7, 129.3, 113.7, 97.4, 73.1, 71.7, 71.5, 65.7, 55.2, 54.3, 47.7.

HRMS(FAB): calcd. for C₁₄H₁₆O₅ [M]⁺ 264.0997, found 264.0997.

1,6-Anhydro-2-azido-2-deoxy-4-O-*p*-methoxybenzyl- β -D-glucopyranose (3):

Epoxide **2** (500 mg, 1.89 mmol) was dissolved in DMF (20 mL) and water (2.2 mL). Sodium azide (738 mg, 11.35-4 mmol) was added. The mixture was heated to 120 °C for 12 h, cooled to r.t. and poured into a mixture of water and Et₂O. The aqueous phase was extracted three times with Et₂O. The combined organic layers were washed with brine, dried with MgSO₄, filtered and the solvent was removed in vacuo. The crude material can be used directly in the next benzylation step or purified using flash chromatography on silica gel (hexanes/EtOAc 1:1) to obtain **3** (441 mg, 1.44 mmol, 76%) as a colorless oil.

¹H NMR (300 MHz, CDCl₃): δ 7.26 (d, *J* = 9.0 Hz, 2H, arom.), 6.85 (d, *J* = 9.0 Hz, 2H, arom.), 5.39 (s, 1H, 1-H), 4.56 (m, 3H, bz), 4.56-4.52 (m, 1H, 5-H), 3.88 (d, *J* = 7.2 Hz, 1H, 6-H₂), 3.81-3.80 (m, 1H, 4-H), 3.76 (s, 3H, OMe), 3.64-3.60 (m, 1H, 6-H₂), 3.30-3.28 (m, 1H, 3-H), 3.16-3.15 (m, 1H, 2-H).

¹³C NMR (75 MHz, CDCl₃): δ 159.2, 129.4, 129.2, 113.8, 100.8, 78.1, 74.9, 71.4, 70.2, 66.1, 62.7, 55.2.

HRMS(FAB): calcd. for C₁₄H₁₆O₅N₃ [M-H]⁺ 306.1090, found 306.1102.

1,6-Anhydro-2-desoxy-4-O-*p*-methoxybenzyl-2-phthalimido- β -D-glucopyranose (4):

Epoxide **2** (40 mg, 0.15 mmol) was dissolved in DMSO (1.5 mL). Phthalimide (85 mg, 0.58 mmol) and potassium phthalimide (84 mg, 0.45 mmol) were added. The mixture was refluxed for 24 h, cooled to r.t. and poured into water and Et₂O. The aqueous phase was extracted three times with Et₂O. The combined organic layers were washed with cooled 1 M NaOH and then with brine, dried with MgSO₄, filtered and the solvent was removed in vacuo. Flash chromatography on silica gel (hexanes/EtOAc 1:1) afforded **4** (26 mg, 0.067 mmol, 45%) as a colorless oil.

¹H NMR (300 MHz, CDCl₃): δ 7.87-7.83, 7.75-7.70, 7.29-7.24 (m, 6H, arom.), 6.85 (m, 2H, arom.), 5.53 (s, 1H, 1-H), 4.66-4.55 (m, 3H, bz, 5-H), 4.32-4.27 (m, 1H, 3-H), 4.06 (d, *J* = 9.9 Hz, 1H, 2-H), 3.78 (s, 3H, OMe), 3.72-3.70 (m, 2H, 6-H₂), 3.37 (d, *J* = 7.5 Hz, 1H, 4-H).

¹³C NMR (75 MHz, CDCl₃): δ 159.3, 134.1, 131.6, 129.5, 123.7, 123.4, 114.0, 102.0, 84.9, 76.4, 72.1, 68.6, 68.1, 57.7, 55.3.

HRMS(FAB): calcd. for C₂₂H₂₂NO₇ [M+H]⁺ 412.1396, found 412.1404.

2-O-Allyl-1,6-anhydro-4-O-*p*-methoxybenzyl- β -D-glucopyranose (5):

Epoxide **2** (1.17 g, 4.44 mmol) was dissolved in DME (50 mL) and cooled to 0 °C. Allyl alcohol (6.04 mL, 88.8 mmol) and NaH (1.78 g, 44.4 mmol, 60 % in mineral oil) were added. The reaction mixture was refluxed for 1 h. Water and EtOAc were added and the aqueous phase was extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried with MgSO₄, filtered, and the solvents were evaporated. Flash chromatography on silica gel (hexanes/EtOAc 1:1) afforded **5** (1.29 g, 4.15 mmol, 93%) as a colorless oil.

¹H NMR (300 MHz, CDCl₃): δ 7.27 (d, *J* = 8.4 Hz, 2H, arom.), 6.87 (d, *J* = 8.5 Hz, 2H, arom.), 5.92 (m, 1H, allyl), 5.42 (s, 1H, 1-H), 5.32-5.18 (m, 2H, allyl), 4.60 (m, 2H, bz), 4.49 (d, *J* = 4.8 Hz, 1H, 5-H), 4.12 (m, 2H, allyl), 3.78-3.76 (m, 5H, OMe, 6-H₂, 3-H), 3.61 (dd, *J* = 5.1, 7.2 Hz, 1H, 6-H₂), 3.28 (d, *J* = 4.5 Hz, 1H, 4-H), 3.19 (d, *J* = 4.5 Hz, 1H, 2-H).

¹³C NMR (75 MHz, CDCl₃): δ 159.1, 134.2, 129.7, 129.3, 117.7, 113.7, 101.1, 79.3, 79.2, 75.3, 71.4, 71.2, 70.5, 66.5, 55.2.

HRMS(FAB): calcd. for C₁₇H₂₁O₆ [M-H]⁺ 321.1338, found 321.1332.

1,6-Anhydro-2-O-benzoyl-4-O-*p*-methoxybenzyl- β -D-glucopyranose (6):

Epoxide **2** (30 mg, 0.11 mmol) was dissolved in DMF (2 mL). Benzoic acid (96 mg, 0.78 mmol) and potassium benzoate (108 mg, 0.67 mmol) were added. The mixture was refluxed for 24 h, cooled down to r.t. and poured into a mixture of sat. NaHCO₃ and Et₂O. The aqueous phase was extracted three times with Et₂O. The combined organic layers were washed with brine, dried with MgSO₄, filtered and the solvent was removed in vacuo. Flash chromatography on silica gel (hexanes/EtOAc 2:1 → 1:1) afforded **6** (31 mg, 0.08 mmol, 73%) as a colorless oil.

¹H NMR (300 MHz, CDCl₃): δ 8.07-6.79 (m, 9H, arom.), 5.58 (s, 1H, 1-H), 4.77-4.76 (m, 1H, 2-H), 4.66 (d, *J* = 5.0 Hz, 1H, bz), 4.60 (m, 1H, bz, 5-H), 4.04 (d, *J* = 8.4 Hz, 1H, 6-H₂), 3.97 (m, 1H, 3-H), 3.77-3.72 (m, 4H, OMe, 6-H₂), 3.44-3.43 (m, 1H, 4-H).

¹³C NMR (75 MHz, CDCl₃): δ 166.1, 159.1, 133.3, 129.9, 129.6, 129.4, 129.2, 128.3, 113.7, 99.8, 77.8, 75.1, 73.6, 71.2, 70.0, 66.0, 55.3.

HRMS(FAB): calcd. for C₂₁H₂₁O₇ [M-H]⁺ 385.1287, found 385.1303.

1,6;2,3-Dianhydro-4-O-benzyl- β -D-talopyranose (7):

1,6-Anhydro-2-iodo-2-deoxy-galactose² (1.10 g, 4.04 mmol) was dissolved in DMF (25 mL) and cooled to 0 °C. Benzyl bromide (1.44 mL, 12.13 mmol) and NaH (485 mg, 12.13 mmol, 60 % in mineral oil) were added. After 1 h, water and Et₂O were added carefully. The aqueous phase was extracted three times with Et₂O. The combined organic layers were washed with brine, dried with MgSO₄, filtered and the solvent was removed in vacuo. Flash chromatography on silica gel (hexanes/acetone 3:2) afforded the epoxide **7** (826 mg, 3.51 mmol, 87%) as a colorless oil.

¹H NMR (300 MHz, CDCl₃): δ 7.37-7.28 (m, 5H, arom.), 5.63 (d, *J* = 3.3 Hz, 1H, 1-H), 4.81 (d, *J* = 11.7 Hz, 1H, bz), 4.66 (d, *J* = 11.9 Hz, 1H, bz), 4.36-4.32 (m, 1H, 5-H), 4.11 (dd, *J* = 1.2, 7.2 Hz, 1H, 6-H₂), 4.00-3.97 (m, 1H, 4-H), 3.58-3.52 (m, 2H, 2-H, 6-H₂), 3.29-3.27 (m, 1H, 3-H).

¹³C NMR (75 MHz, CDCl₃): δ 137.4, 128.3, 127.8, 127.5, 96.9, 72.4, 71.0, 69.0, 63.4, 57.2, 47.9.

HRMS(FAB): calcd. for C₁₃H₁₄O₄ [M]⁺ 234.0892, found 234.0898.

1,6-Anhydro-4-O-benzyl-2-deoxy-2-phthalimido- β -D-galactopyranose (8):

Epoxide **7** (175 mg, 0.75 mmol) was dissolved in DMSO (4 mL). Phthalimide (413 mg, 2.81 mmol) and potassium phthalimide (413 mg, 2.23 mmol) were added. The mixture was heated to 160 °C for 20 h, cooled down to r.t. and poured onto water and Et₂O. The aqueous phase was extracted three times with Et₂O. The combined organic layers were washed twice with 1 M NaOH (0 °C) and then with brine, dried with MgSO₄, filtered, and the solvent was removed in vacuo. Flash chromatography on silica gel (hexanes/acetone 3:1) afforded **8** (180 mg, 0.47 mmol, 63%) as a colorless powder.

¹H NMR (300 MHz, CDCl₃): δ 7.86-7.81 (m, 2H, arom.), 7.72-7.70 (m, 2H, arom.), 7.37-7.35 (m, 5H, arom.), 5.30 (m, 1H, 1-H), 4.82-4.69 (m, 3H, bz, 4-H), 4.52 (m, 1H, 5-H), 4.44-4.43 (m, 2H, 2-H, 3-H), 4.36 (dd, *J* = 7.2 Hz, 1H, 6-H₂), 3.68-3.64 (m, 1H, 6-H₂).

¹³C NMR (75 MHz, CDCl₃): δ 167.6, 137.2, 134.2, 131.4, 128.5, 128.2, 127.8, 127.7, 123.2, 101.0, 72.7, 72.4, 72.0, 65.7, 64.0, 56.2.

HRMS(FAB): calcd. for C₂₁H₂₀O₆N [M+H]⁺ 382.1291, found 382.1273.

6-O-Acetyl-2-azido-3-O-benzyl-2-deoxy-4-O-*p*-methoxybenzyl- β -D-glucopyranose trichloroacetimidate (9):

1,6-Anhydro-2-azido-3-O-benzyl-2-deoxy-4-O-*p*-methoxybenzy- β -D-glucopyranose:

Alcohol **3** (21 mg, 0.068 mmol), benzyl bromide (20 μ L, 0.17 mmol) and NaH (7.0 mg, 0.17 mmol, 60 % in mineral oil) were dissolved in DMF (2 mL). After 1.5 h, sat. aq. NH_4Cl and Et_2O were added carefully. The aqueous phase was extracted three times with Et_2O . The combined organic layers were washed with brine, dried with MgSO_4 , filtered and the solvent was removed in vacuo. Flash chromatography on silica gel (hexanes/EtOAc 3:1) afforded the benzylether (22 mg, 0.056 mmol, 81%) as a colorless oil.

^1H NMR (300 MHz, CDCl_3): δ 7.37-7.25 (m, 7H, arom.), 6.89 (d, J = 6.6 Hz, 2H, arom.), 5.48 (s, 1H 1-H), 4.61-4.48 (m, 5H, 2 x bz, 5-H), 4.00 (dd, J = 6.9, 0.9 Hz, 1H, 6- H_2), 3.81 (s, 3H, OMe), 3.71 (dd, J = 6.0, 6.9 Hz, 1H, 6- H_2), 3.63 (m, 1H, 3-H), 3.37 (m, 1H, 4-H), 3.27 (m, 1H, 2-H).

^{13}C NMR (75 MHz, CDCl_3): δ 159.2, 137.1, 129.4, 129.2, 128.4, 127.9, 127.7, 113.7, 100.4, 76.1, 75.3, 74.4, 72.3, 71.8, 70.9, 65.3, 55.3.

HRMS(FAB): calcd. for $\text{C}_{21}\text{H}_{22}\text{N}_3\text{O}_5$ $[\text{M}-\text{H}]^+$ 396.1559, found 396.1569.

1,6-O-Diacetyl-2-azido-3-O-benzyl-2-deoxy-4-O-*p*-methoxybenzy-D-glucopyranose:

The 1,6-anhydro-compound from the preceding step (343 mg, 0.863 mmol) was dissolved in Ac_2O (15 mL) and cooled to -65°C . $\text{BF}_3\cdot\text{Et}_2\text{O}$ (60 μ L) was added. After 2 h, the reaction mixture was diluted with CH_2Cl_2 and sat. aq. NaHCO_3 . The aqueous layer was extracted twice with CH_2Cl_2 . The combined organic layers were washed with ice water, dried with MgSO_4 , and the solvent was removed in vacuo. Flash chromatography on silica gel (hexanes/EtOAc 3:1) afforded the ring opened product (415 mg, 0.831 mmol, 96%) as a colorless oil (anomeric mixture α/β = 8:1). α -Anomer:

^1H NMR (300 MHz, CDCl_3): δ 7.39-7.34 (m, 5H, arom.), 7.19 (d, J = 7.2 Hz, 2H, arom.), 6.85 (d, J = 7.2 Hz, 2H, arom.), 6.20 (s, 1H 1-H), 4.91 (m, 2H, bz), 4.77 (d, J = 10.5 Hz, 1H, bz), 4.50 (d, J = 10.5 Hz, 1H, bz), 4.23 (m, 2H, 6- H_2), 3.97-3.90 (m, 2H, 3-H, 5-H), 3.78 (s, 3H, OMe), 3.63-3.56 (m, 2H, 2-H, 4-H), 2.13 (s, 3H, CH_3), 2.02 (s, 3H, CH_3).

^{13}C NMR (75 MHz, CDCl_3): δ 170.4, 168.6, 159.4, 137.3, 129.7, 129.2, 128.5, 128.0, 127.9, 113.9, 90.3, 80.5, 76.7, 75.6, 74.9, 71.3, 62.7, 62.3, 55.3, 21.0, 20.9.

HRMS(FAB): calcd. for $\text{C}_{25}\text{H}_{28}\text{N}_3\text{O}_8$ $[\text{M}-\text{H}]^+$ 498.1876, found 498.1884.

6-O-Acetyl-2-azido-3-O-benzyl-2-deoxy-4-O-*p*-methoxybenzyl- β -D-glucopyranose trichloroacetimidate (9):

The 1-O-acetyl compound (300 mg, 0.602 mmol) was dissolved in Et_2O (5 mL) and cooled to 0°C . Benzyl amine (2 mL) was added. After 3.5 h, the mixture was treated with HCl (1M) and the aqueous layer was washed three times with EtOAc. The combined organic layers were washed with water, dried with MgSO_4 , and the solvent was removed in vacuo. The crude material was dissolved in CH_2Cl_2 (5 mL). Powdered molecular sieves 4 \AA (540 mg), potassium carbonate (249 mg, 1.80 mmol) and trichloroacetonitrile (361 μ L, 3.60 mmol) were added. After 12 h, the mixture was filtered through Celite. Flash chromatography on silica gel (hexanes/EtOAc 3:1, 1% TEA) afforded the imidate **9** (271 mg, 0.452 mmol, 75%) as a colorless oil (anomeric mixture α/β = 1:10). β -Anomer:

^1H NMR (300 MHz, CDCl_3): δ 8.71 (s, 1H, NH), 7.39-7.33 (m, 5H, arom.), 7.17 (d, J = 8.7 Hz, 2H, arom.), 6.84 (d, J = 8.7 Hz, 2H, arom.), 5.59 (d, J = 9.0 Hz, 1H, 1-H), 4.90-4.85 (m, 2H, bz), 4.76 (d, J = 10.5 Hz, 1H, bz), 4.50 (d, J = 10.5 Hz, 1H, bz), 4.23 (m, 2H, 6- H_2), 3.78 (s, 3H, OMe), 3.67-3.56 (m, 2H, 2-H, 3-H, 4-H, 5-H), 2.01 (s, 3H, CH_3).

^{13}C NMR (75 MHz, CDCl_3): δ 160.8, 137.5, 129.8, 129.3, 128.5, 128.0, 113.9, 96.6, 83.1, 76.2, 75.7, 74.7, 73.9, 65.8, 62.4, 55.3, 20.9.

HRMS(FAB): calcd. for $\text{C}_{25}\text{H}_{27}\text{O}_7\text{N}_4\text{Cl}_3$ $[\text{M}]^+$ 600.0946, found 600.0928.

Methyl (phenyl 2-O-allyl-3-O-benzyl-1-thio- α -D-glucopyranoside) uronate (10):

2-O-Allyl-1,6-anhydro-3-O-benzyl-4-O-*p*-methoxybenzyl- β -D-glucopyranose:

Alcohol **5** (1.20 g, 3.72 mmol), benzyl bromide (886 μ L, 7.45 mmol) and NaH (298 mg, 7.45 mmol, 60 % in mineral oil) were dissolved in DMF (40 mL). After 45 min water and Et_2O were added carefully. The aqueous phase was extracted three times with Et_2O . The combined organic layers were washed with brine, dried with MgSO_4 , filtered and the solvent was removed in vacuo. Flash chromatography on silica gel (hexanes/EtOAc 3:1) afforded the benzylether (1.28 g, 3.09 mmol, 83%) as a colorless oil.

^1H NMR (300 MHz, CDCl_3): δ 7.36-7.25 (m, 7H, arom.), 6.85 (d, J = 6.6 Hz, 2H, arom.), 5.85 (m, 1H, allyl), 5.43 (s, 1H 1-H), 5.26-5.15 (m, 2H, allyl), 4.56-4.48 (m, 5H, 2 x bz, 5-H), 4.02-3.99 (m, 2H, allyl), 3.88 (d, J = 7.2 Hz, 1H, 6- H_2), 3.79 (s, 3H, OMe), 3.65 (dd, J = 6.0, 7.2 Hz, 1H, 6- H_2), 3.53 (m, 1H, 3-H), 3.31-3.30 (m, 2H, 2-H, 4-H).

^{13}C NMR (75 MHz, CDCl_3): δ 159.1, 137.8, 134.3, 129.8, 129.3, 127.7, 127.6, 117.6, 113.7, 100.5, 76.4, 76.2, 76.1, 74.4, 72.1, 71.0, 70.8, 65.5, 55.3.
HRMS(FAB): calcd. for $\text{C}_{24}\text{H}_{27}\text{O}_6$ $[\text{M}-\text{H}]^+$ 411.1808, found 411.1811.

Phenyl 2-O-allyl-3-O-benzyl-4-O-*p*-methoxybenzyl-1-thio- α -D-glucopyranose:

The 1,6 anhydro compound from the preceding step (950 mg, 2.30 mmol) was dissolved in CH_2Cl_2 (35 mL) and cooled to 0 °C. ZnI_2 (2.57 g, 8.05 mmol) and TMSSPh (1.52 mL, 8.05 mmol) were added. The reaction mixture was stirred for 2.5 h (0 °C \rightarrow r.t.). Sat. aq. NaHCO_3 solution was added. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried with MgSO_4 , filtered and the solvent was removed in vacuo. The residue was dissolved in THF (6 mL) and TBAF (3 mL of a 1 M solution in THF) was added. After 30 min, the solvent was evaporated and the residue was diluted with water and EtOAc. The aqueous phase was extracted three times with EtOAc. The combined organic layers were washed with brine, dried with MgSO_4 , filtered and the solvent was removed in vacuo. Flash chromatography on silica gel (hexanes/EtOAc 3:1 \rightarrow 1:1) afforded the 1-thio glucopyranose (1.009–0.1 g, 1.93 mmol, 84%; α/β = 3:1) as a colorless oil. The anomeric isomers can be readily separated.

α -Anomer ^1H NMR (300 MHz, CDCl_3): δ 7.47–7.19 (m, 12H, arom.), 6.85 (d, J = 9.0 Hz, 2H, arom.), 6.00–5.83 (m, 1H, allyl), 5.66 (d, J = 5.1 Hz, 1H, 1-H), 5.35–5.18 (m, 2H, allyl), 4.98 (d, J = 10.5 Hz, 1H, bz), 4.80 (d, J = 10.6 Hz, 2H, bz), 4.56 (d, J = 10.5 Hz, 1H, bz), 4.23–4.13 (m, 3H, allyl, 5-H), 3.87–3.79 (m, 1H, 6- H_2), 3.78–3.77 (m, 4H, 2-H, OMe), 3.69 (m, 2H, 3-H, 4-H), 3.53 (dd, J = 9.9, 9.7 Hz, 1H, 6- H_2).

^{13}C NMR (75 MHz, CDCl_3): δ 159.2, 138.5, 134.2, 133.9, 131.7, 130.0, 129.6, 128.9, 128.3, 127.9, 127.6, 127.2, 117.9, 113.8, 86.7, 82.3, 79.7, 76.6, 75.7, 74.7, 71.8, 71.7, 61.8, 55.3.

HRMS(FAB): calcd. for $\text{C}_{30}\text{H}_{33}\text{O}_6\text{S}$ $[\text{M}]^+$ 521.1998, found 521.2013.

β -Anomer ^1H NMR (300 MHz, CDCl_3): δ 7.48–7.16 (m, 12H, arom.), 6.83 (d, J = 8.7 Hz, 2H, arom.), 6.00–5.89 (m, 1H, allyl), 5.30–5.15 (m, 2H, allyl), 4.88–4.52 (m, 5H, bz, 1-H), 4.39–4.20 (m, 2H, allyl), 3.78–3.77 (m, 4H, 5-H, OMe), 3.64–3.60 (m, 2H, 3-H, 6- H_2), 3.52–3.45 (m, 1H, 6- H_2), 3.35–3.31 (m, 2H, 2-H, 4-H).

tert-Butyl (phenyl 2-O-allyl-3-O-benzyl-4-O-*p*-methoxybenzyl-1-thio- α -D-glucopyranoside) uronate :

The alcohol from the preceding step (α -isomer) (50.48 mg, 0.093 mmol), pyridinium dichromate (70 mg, 0.186–0.19 mmol), Ac_2O (88 μL , 0.93 mmol) and *t*BuOH (178 μL , 1.86 mmol) were dissolved in CH_2Cl_2 (2 mL). After 5 h, the reaction mixture was poured onto a silica gel column (EtOAc, 5 cm layer of EtOAc above the silica gel). After 15 min, the product was eluted and the solvents were removed in vacuo. Flash chromatography on silica gel (hexanes/acetone 3:1) afforded the ester (47 mg, 0.079 mmol, 85%) as a colorless oil.

^1H NMR (300 MHz, CDCl_3): δ 7.57–7.52 (m, 2H, arom.), 7.37–7.25 (m, 8H, arom.), 7.19 (d, J = 8.6 Hz, 2H, arom.), 6.83 (d, J = 8.4 Hz, 2H, arom.), 6.00–5.88 (m, 1H, allyl), 5.67 (br s, 1H, 1-H), 5.36–5.19 (m, 2H, allyl), 4.98 (d, J = 11.1 Hz, 1H, bz), 4.81–4.76 (m, 2H, bz), 4.68–4.61 (m, 2H, bz, 5-H), 4.23–4.17 (m, 2H, allyl), 3.84–3.78 (m, 6H, 2-H, 3-H, 4-H, OMe), 1.47 (s, 9H, *t*-Bu).

^{13}C NMR (75 MHz, CDCl_3): δ 168.3, 159.0, 138.4, 134.0, 133.3, 132.5, 130.2, 129.3, 128.7, 128.2, 127.8, 127.5, 127.4, 117.9, 113.6, 87.4, 82.0, 81.6, 79.1, 78.6, 75.7, 74.8, 71.7, 71.7, 55.2, 27.9.

HRMS(FAB): calcd. for $\text{C}_{34}\text{H}_{41}\text{O}_7\text{S}$ $[\text{M}+\text{H}]^+$ 593.2573, found 593.2562.

Methyl (phenyl 2-O-allyl-3-O-benzyl-1-thio- α -D-glucopyranoside) uronate (**10**):

The ester from the preceding step (20 mg, 0.034 mmol) was dissolved in MeOH (2 mL), cooled to 0 °C, and acetyl chloride (146 μL , 2.04 mmol) was added dropwise. After 12 h, the solvent was evaporated. Flash chromatography on silica gel (hexanes/EtOAc 3:1) afforded alcohol **10** (11 mg, 0.026 mmol, 76%) as a colorless solid.

^1H NMR (300 MHz, CDCl_3): δ 7.62–7.58 (m, 2H, arom.), 7.32–7.25 (m, 8H, arom.), 6.00–5.88 (m, 1H, allyl), 5.82 (d, J = 2.1 Hz, 1H, 1-H), 5.34–5.20 (m, 2H, allyl), 4.73–4.71 (m, 3H, bz, 5-H), 4.20–4.17 (m, 2H, allyl), 4.13–4.07 (m, 1H, 4-H), 3.82–3.77 (m, 2H, 2-H, 3-H), 3.68 (s, 3H, Me).

^{13}C NMR (75 MHz, CDCl_3): δ 169.8, 137.6, 134.2, 133.5, 130.5, 128.8, 128.3, 127.8, 127.6, 126.9, 118.6, 84.3, 77.4, 76.2, 74.2, 73.7, 72.3, 69.1, 52.3.

HRMS(FAB): calcd. for $\text{C}_{23}\text{H}_{27}\text{O}_6\text{S}$ $[\text{M}+\text{H}]^+$ 431.1528, found 431.1526.

6'-O-Acetyl-2'-azido-3'-O-benzyl-2'-deoxy-4'-O-*p*-methoxybenzyl- α -D-glucopyranosyl (1 \rightarrow 4)-methyl (phenyl 2-O-allyl-3-O-benzyl-1-thio- α -D-glucopyranoside)uronate (11**):**

Glycosyl acceptor **10** (26 mg, 0.060 mmol) and glycosyl donor **9** (48 mg, 0.080 mmol) were coevaporated twice in toluene and then dissolved in toluene (5 mL). Powdered molecular sieves 4 Å (100 mg) were added. After 30 min, the mixture was cooled to –78 °C and TMSOTf (120 μL of a freshly prepared 0.1 M solution in toluene) was added. After 7

h (−78°C → r.t.), TEA (0.5 mL) was added. The mixture was filtered through Celite and the solvent was evaporated. Flash column chromatography on silica gel (hexanes/EtOAc 3:1) yielded **11** (47 mg, 0.054 mmol, 90%) as a colorless powder. The β-anomer was not observed.

¹H NMR (300 MHz, CDCl₃): δ 7.50-7.49 (m, 2H, arom.), 7.41-7.25 (m, 13H, arom.), 7.16 (d, *J* = 8.7 Hz, 2H, arom.), 6.82 (d, *J* = 8.7 Hz, 2H, arom.), 5.98-5.75 (m, 1H, allyl), 5.67 (d, *J* = 4.5 Hz, 1H, 1-H), 5.50 (d, *J* = 3.9 Hz, 1H 1'-H), 5.34-5.18 (m, 2H, allyl), 5.00 (d, *J* = 10.5 Hz, 1H, bz), 4.90-4.73 (m, 5H, bz, 5-H), 4.47 (d, *J* = 10.5 Hz, 1H, bz), 4.20-4.07 (m, 6H, allyl, 6'-H₂, 4-H, 3-H), 3.93-3.84 (m, 2H, 3'-H, 2-H), 3.78 (s, 3H, OMe), 3.70 (s, 3H, Me), 3.66-3.60 (m, 1H, 5'-H), 3.58-3.47 (m, 1H, 4'-H), 3.28 (dd, *J* = 3.9, 10.5 Hz, 1H, 2'-H), 2.00 (s, 3H, Me).

¹³C NMR (75 MHz, CDCl₃): δ 170.9, 170.6, 169.2, 159.2, 153.2, 138.1, 137.6, 133.8, 133.5, 131.5, 129.5, 128.9, 128.4, 128.2, 127.9, 127.8, 127.5, 127.4, 118.2, 113.8, 97.8, 87.0, 80.7, 80.0, 78.8, 75.4, 75.2, 75.1, 74.5, 71.7, 70.9, 69.7, 63.3, 62.3, 60.4, 55.3, 52.7, 20.9.

HRMS(FAB): calcd. for C₄₆H₅₂N₃O₁₂S [M+H]⁺ 870.3271, found 870.3261.

Methyl (phenyl 2-O-allyl-3-O-benzyl-4-O-triisopropylsilyl-1-thio-α-D-glucopyranoside) uronate (12):

Alcohol **10** (300 mg, 0.696 mmol) was dissolved in CH₂Cl₂ (5 mL) at 0 °C. 2,6-Lutidine (0.326 mL, 2.80 mmol) and TIPSOTf (0.376 mL, 1.40 mmol) were added. After 6 h, sat. aq. NaHCO₃ was added. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried with MgSO₄, and the solvent removed in vacuo. Flash chromatography on silica gel (hexanes/CH₂Cl₂ 1:3) afforded the compound **12** (373 mg, 0.635 mmol, 91%) as a colorless solid.

¹H NMR (300 MHz, CDCl₃): δ 7.52-7.49 (m, 2H, arom.), 7.31-7.24 (m, 8H, arom.), 5.91-5.87 (m, 1H, allyl), 5.67 (d, *J* = 4.8 Hz, 1H, 1-H), 5.26-5.04 (m, 3H, allyl, 5-H), 4.69 (d, *J* = 10.5 Hz, 1H, bz), 4.61 (d, *J* = 10.9 Hz, 1H, bz), 4.13-4.01 (m, 3H, allyl, 4-H), 3.83-3.80 (m, 1H, 2-H), 3.71 (s, 3H, Me), 3.67-3.64 (m, 1H 3-H), 1.03 (m, 21H, TIPS).

¹³C NMR (75 MHz, CDCl₃): δ 169.8, 138.8, 134.0, 131.7, 128.9, 128.2, 127.9, 127.3, 126.9, 118.1, 87.1, 81.0, 79.5, 74.4, 73.4, 71.8, 71.5, 52.3, 18.2, 13.1.

HRMS(FAB): calcd. for C₃₂H₄₇O₆SiS [M+H]⁺ 587.2863, found 587.2884.

Methyl 2'-O-allyl-3'-O-benzyl-4'-O-triisopropylsilyl-β-D-glucopyranosyluronate-(1→3)-1,6-O-acetyl-4-O-benzyl-2-deoxy-2-phthalimido-D-galactopyranose (13):

Methyl 2'-O-allyl-3'-O-benzyl-4'-O-triisopropylsilyl-β-D-glucopyranosyluronate-(1→3)-1,6-dianhydro-4-O-benzyl-2-deoxy-2-phthalimido-β-D-galactopyranose:

Glycosyl acceptor **8** (16 mg, 0.042 mmol) and glycosyl donor **12** (35 mg, 0.060 mmol) were coevaporated twice in toluene and then dissolved in CH₂Cl₂ (0.25 mL) and CH₃CN (1.5 mL). Powdered molecular sieves 4 Å (125 mg) and, after 30 min, NIS (17 mg, 0.078) were added. The mixture was stirred for 5 min and cooled to −40°C. After 10 min, TFA (50 μL of a freshly prepared 0.2 M solution in CH₂Cl₂) was added slowly. After 3 h (−40°C → r.t.), TEA (0.5 mL) was added. The mixture was filtered through Celite and the solvent was evaporated. The residue was dissolved in EtOAc and solutions of Na₂S₂O₃ (1M) and NaHCO₃ (sat.) were added. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried with MgSO₄, and the solvent was removed in vacuo. Flash column chromatography on silica gel (hexanes/EtOAc 4:1) yielded the β(1→3)-disaccharide (21 mg, 0.025 mmol, 60%) as a colorless oil. A minor amount of the α-isomer (3.5 mg, 0.0041 10%) was also obtained.

¹H NMR (500 MHz, CDCl₃): δ 7.85-7.74 (m, 4H), 7.40-7.20 (m, 10H), 5.83-5.79 (m, 1H), 5.34 (m, 1H), 5.20 (d, 1H), 5.04 (m, 2H), 4.91 (d, 1H), 4.73-4.71 (m, 1H), 4.66 (m, 1H), 4.59-4.48 (m, 5H), 4.15-3.96 (m, 3H), 3.81 (d, 1H), 3.74-3.72 (m, 2H), 3.61-3.56 (m, 1H), 3.56 (s, 3H), 3.44-3.41 (m, 2H), 0.99-0.96 (m, 21H).

¹³C NMR (75 MHz, CDCl₃): δ 168.7, 167.6, 138.7, 137.2, 137.0, 134.2, 131.4, 128.2, 128.1, 128.0, 127.9, 127.5, 127.0, 126.8, 123.4, 116.9, 102.6, 101.3, 83.9, 81.6, 74.3, 73.5, 73.1, 72.4, 71.9, 71.3, 71.2, 64.1, 55.4, 52.0, 18.2, 13.1.

HRMS(FAB): calcd. for C₄₇H₆₀NO₁₂Si [M+H]⁺ 858.3885, found 858.3910.

Methyl 2'-O-allyl-3'-O-benzyl-4'-O-triisopropylsilyl-β-D-glucopyranosyluronate-(1→3)-1,6-O-acetyl-4-O-benzyl-2-deoxy-2-phthalimido-D-galactopyranose (13):

The β(1→3)-disaccharide (3.0 mg, 3.5 μmol) was dissolved in Ac₂O (0.5 mL) and cooled to 0°C. TFA (25 μL) was added. The solvent was evaporated after 2 h. Toluene was added to the residue and removed again in vacuo. This was repeated three times. Flash column chromatography on silica gel (hexanes/EtOAc 3:1) yielded compound **13** (2.8 mg, 2.9 μmol, 83%) as a colorless oil (anomeric mixture α/β 1:1).

¹H NMR (500 MHz, CDCl₃): δ 7.82-7.71 (m, 14H, arom.), 6.23 (d, 0.5H, *J* = 3.5 Hz), 6.12 (d, 0.5H, *J* = 6.5 Hz), 5.30-5.21 (m, 1H), 5.09-5.06 (m, 0.5H), 4.98-4.94 (m, 1H), 4.85-4.69 (m, 4H), 4.62-4.55 (m, 1H), 4.49-4.36 (m, 2H), 4.21-4.05 (m, 4H), 3.97-3.87 (m, 3.5H), 3.78-3.66 (m, 4H), 3.38 (t, 0.5H), 3.28 (t, 0.5H), 3.19-3.14 (m, 1H), 2.02 (s, 1.5H), 1.93 (m, 4.5H), 0.94-0.92 (m, 21H) .

¹³C NMR (125 MHz, CDCl₃): δ 170.1, 168.0, 167.1, 138.5, 138.4, 134.2, 134.0, 133.9, 128.8, 128.7, 128.3, 128.0, 127.7, 127.2, 126.9, 123.7, 123.6, 123.2, 115.8, 115.2, 104.4, 104.1, 91.9, 90.8, 83.6, 83.2, 82.0, 81.5, 74.8, 74.7, 74.6, 74.5, 74.2, 74.0, 73.9, 73.2, 72.8, 72.7, 72.6, 72.2, 71.9, 71.0, 63.0, 62.9, 52.2, 51.5, 50.8, 29.7, 20.9, 20.8, 20.7, 18.1, 18.0, 13.1, 13.0.

HRMS(FAB): calcd. for C₅₁H₆₄NO₁₅Si [M-H]⁺ 958.4045, found 958.4060.

References

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